

Comparison of Longitudinal and Cross-sectional Cortical Thickness Measurements

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Introduction: In multiple sclerosis (MS), there is substantial cortical pathology^[1]. Conventional MRI has a limited capability in detecting cortical abnormalities. Advanced imaging techniques such as high-field MRI and double inversion recovery enable detection of some types of cortical lesions but not all^[1]. Cortical atrophy reflects the net effects of all types of MS pathologic processes in the cortex. New sophisticated image processing tools allow measurements of cortical thickness (CTh) in MS^[2], and its temporal change is clinically relevant^[3]. However, changes in CTh are small (approximately 0.01mm/yr^[3-5]). Thus, CTh measurements require consistency and high reproducibility. Recently, a new CTh measurement algorithm called CLADA (Cortical Longitudinal Atrophy Detection Algorithm) was developed for analysis of serial MRIs from patients with MS^[5]. CLADA achieves longitudinal processing by (1) creation of unbiased subject-specific template image by intra-subject registration and averaging, (2) generation of explicit dual-surface model using the averaged template image, (3) deformation of the surface model to images from individual time points, and (4) calculation of global and regional (frontal, temporal, parietal, and occipital lobes) CTh for each image. The potential benefits of longitudinal over cross-sectional processing (where each MRI is independently analyzed) using CLADA have not been determined.

Objectives: The objectives in the current study were to (1) compare full longitudinal version of CLADA to a cross-sectional version of CLADA in terms of scan-rescan reproducibility errors; and (2) determine which version of CLADA is superior.

Methods: *MRI:* We used 2 datasets of MRIs to calculate the reproducibility errors. The first was high-resolution MPRAGE [slice thickness (THK)=1.2mm; number of slices (no. slice)=128; matrix size=256×256; in-plane resolution (IPR)= 1×1mm] from 18 MS patients (3 MRIs within 2 weeks). The second was T1-weighted spin echo images (T1SE) [THK=3mm; no. slice=48; matrix size= 256×192; IPR=0.9×0.9mm] obtained from 9 MS patients (3 MRIs within 2 weeks). *Image Analysis:* We applied both full longitudinal and cross-sectional versions of CLADA on the 2 datasets. In the full longitudinal CLADA, all 3 MRIs were used to create the initial deformable model, whereas in the cross-sectional version, each MRI was analyzed independently without intra-subject registration, averaging, and longitudinal deformation. *Statistical Analysis:* The scan-rescan reproducibility error was defined as the mean absolute deviation ($MAD = \sum |CTh_n - \mu_{CTh}|/3$ where $n=1,2,3$ and μ_{CTh} was the average of 3 time points); the percent error was calculated by $MAD / \mu_{CTh} \times 100\%$. We also used t-tests to compare the reproducibility error in global and regional CTh.

Results: Fig. 1 shows the plot of scan-rescan errors in global CTh for each patient from full longitudinal and cross-sectional methods, showing full CLADA had lower reproducibility errors for 22 out of 27 cases studied (81%). Fig. 2 shows boxplots of global and regional percent errors from both methods. Mean regional errors were consistently (and often significantly) higher in the cross-sectional version than in full CLADA.

Conclusion: CLADA effectively reduces measurement error through longitudinal processing. Since changes in CTh are small, the reduced errors will improve the reliability of cortical atrophy estimates in MS and other neurodegenerative diseases.

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References: [1] Geurts et al. *Lancet Neurology* 2008. [2] Sailer et al. *Brain* 2003. [3] Chen et al. *NeuroImage* 2004. [4] Sampat et al. *Proc. American Academy of Neurology* 2010. [5] Nakamura et al. *NeuroImage* 2010 *in press*.

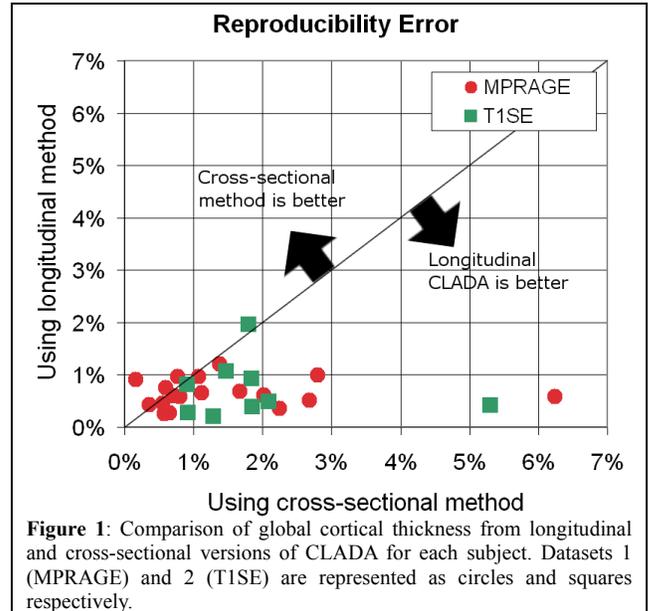


Figure 1: Comparison of global cortical thickness from longitudinal and cross-sectional versions of CLADA for each subject. Datasets 1 (MPRAGE) and 2 (T1SE) are represented as circles and squares respectively.

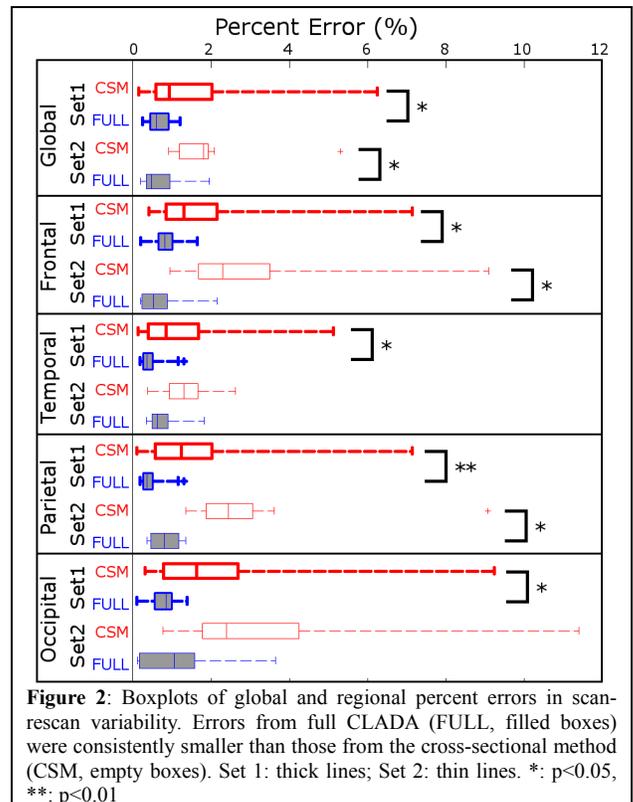


Figure 2: Boxplots of global and regional percent errors in scan-rescan variability. Errors from full CLADA (FULL, filled boxes) were consistently smaller than those from the cross-sectional method (CSM, empty boxes). Set 1: thick lines; Set 2: thin lines. *: $p < 0.05$, **: $p < 0.01$